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ENVIRONMENTAL STIMULUS CONTROL OF DRUG TAKING BEHAVIOR

LEVEL II

Final Report

May 1979
(for the period June 1974 to Nov 1975)

Douglas P. Ferraro

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Two Macaca mulatta and one Macaca java monkeys were trained to press a key for food pellets on a differential reinforcement of low rate (DRL) schedule which required consecutive key-press responses to be spaced at least 20 sec apart in order to produce reinforcement. When behavior had stabilized, the monkeys were administered either 0.0, 0.05, 0.10, .025, or 0.50 mg/kg of cocaine i.v. during daily sessions. Cocaine produced a bi-component, dose-related complete cessation of responding which began and ended abruptly. Following this post-

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infusion pause, a dose-related behavioral disruption in the form of shortened inter-response times was observed.

ABSTRACT

Two Macaca mulatta and one Macaca java monkeys were trained to press a key for food pellets on a differential reinforcement of low rate (DRL) schedule which required consecutive key-press responses to be spaced at least 20 sec apart in order to produce reinforcement. When behavior had stabilized, the monkeys were administered either 0.0, 0.05, 0.10, 0.25, or 0.50 mg/kg of cocaine i.v. during daily sessions. Cocaine produced a bi-component, dose-dependent effect. Immediately following cocaine infusion there was a dose-related complete cessation of responding which began and ended abruptly. Following this post-infusion pause, a dose-related behavioral disruption in the form of shortened inter-response times was observed.

FOREWORD

This research was carried out under Contract No. DAMD 17-74-C-4097 from the U.S. Army Medical Research and Development Command. The author acknowledges the supervision of Captain Kenneth Zych, Project Officer, and the assistance of Charles W. Morrow and Yvonne Parsons.

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council.

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INTRODUCTION

The manner in which cocaine functions to establish and maintain an operant response has been studied extensively. In general, drug self-administration studies have shown that operant response patterns associated with cocaine reinforcement are characteristic of those typically observed with other stimulant-class drug reinforcers (e.g., d-amphetamine, methamphetamine, and pipradol)[1,2,3,4]. By comparison, only limited research has been conducted to assess the effects of cocaine on operant behavior maintained with food or water reinforcement[5,6,7].

A sensitive operant behavioral baseline is achieved by requiring that food reinforcement be contingent upon the occurrence of the first response emitted after some fixed minimum time interval has elapsed since the preceding response. Should a response occur before the minimum interval, the interval is begun again. This schedule is termed differential reinforcement of low response rate (DRL). Stimulant class drugs have been shown to produce a biphasic effect on DRL response rate [8,9]. In general, low doses of stimulants typically reduce the time between responses, while higher doses increase inter-response times. At very high doses, the behavioral disruption induced by stimulant drugs

takes the form of sporadic pauses alternating with sporadic bursts of responding.

We now report an experiment in which the effects of i.v. cocaine on previously established DRL behavior were investigated.

METHOD

Animals

Two adult Macaca mulatta and one male adult Macaca java monkeys, each weighing approximately 6.0 kg, served as subjects. Both Macaca mulatta (T1 and V2) had extensive behavioral and drug experience. However, neither monkey had prior experience on the baseline task or with cocaine. The Macaca java (C3) had a prior history of cocaine self-administration. All monkeys were drug free for three months preceding baseline training for this experiment. Experimental sessions were scheduled seven days a week at the same time daily. The animals were maintained at their ad libitum body weights but were fed only once a day at the end of the experimental session.

Apparatus and Drug

Each monkey was fitted with a Plexiglas helmet which served as a catheter protection system. After each animal had adapted to this restraint, it was surgically prepared with a chronic indwelling venous catheter of siliconized rubber using a sterile technique. The catheter was anchored to deep muscle tissue in the neck with the proximal end passing through the internal jugular vein and terminating in the right atrium of the heart. The distal end was passed

subcutaneously to the top of the head where it exited through a stab wound. This end of the catheter was then connected to a set of fittings in the helmet which allowed the catheter system to be capped or temporarily coupled to an infusion pump during experimental sessions. The infusion pump was set to deliver 1.0 ml of solution over 55 sec.

During experimental sessions the monkeys were restrained in a primate chair and connected to an infusion pump which was located inside a large ventilated, sound-attenuating chamber. A stimulus-response panel containing two horizontally aligned translucent response keys (5.1 cm x 5.1 cm) and a food well located 13.5 cm below the right key was mounted on the primate chair. The right response key was illuminated with a green 3-watt lamp. Reinforcement consisted of a 300 mg banana pellet delivered into the food well.

The drug used was cocaine hydrochloride dissolved in 0.9% physiological saline. Solutions were prepared in concentrations which allowed the appropriate dose to be contained in 0.3 ml of solution. A flush solution of sodium heparin and saline (100 units/ml) was used to push the drug solution through the catheter system into the monkey. The heparin/saline flush solution was also used for nondrug control injections.

Procedure

The monkeys were trained to press the response key with reinforcements made available according to a 20 sec differential reinforcement of low response rate (DRL 20) schedule. Under the DRL 20 schedule, reinforcement was delivered only for a response that followed the immediately preceding response by 20 sec or more. If a response followed the preceding response by less than 20 sec, the interval timer was reset and the 20 sec interval was reinitiated. Daily sessions were as follows. The monkey was transported to the experimental apparatus, restrained in the primate chair, and connected to the infusion apparatus. Illumination of the response key signalled the start of the session. After 25 reinforcements had been obtained, the infusion pump was operated so as to deliver 1.0 ml of flush solution over a 55 sec infusion duration to the monkey. Daily sessions were terminated when monkeys T1 and V2 had obtained 150 reinforcements, or when 125 reinforcements had been obtained by monkey C3. A reduced session criterion for monkey C3 was implemented after repeated attempts failed to obtain stable performance in this animal beyond 130 reinforcements.

The monkeys were run on the baseline task until a stability criterion was achieved. The criterion consisted of at least

three consecutive sessions where median inter-response times did not vary by more than ± 5%. Subsequent to achieving stability on the baseline task, doses of cocaine were administered during daily infusions. All animals received 0.05, 0.10, 0.25, and 0.50 mg/kg of cocaine. Drug sessions were varied with respect to dosage and were separated by at least three consecutive nondrug sessions which met the baseline stability criterion.

RESULTS

In this experiment either cocaine or control solution was infused immediately after the animal had obtained 25 reinforcements. After nondrug control injections, latencies for the first post-infusion response were less than 50 sec. However, all doses of cocaine above 0.05 mg/kg produced an immediate cessation of responding which lasted for longer than 50 sec. The actual durations of these cocaine-induced post-infusion pauses are presented for individual animals in Figure 1. As can be seen therein, a monotonic increase in the duration of the post-infusion pause was obtained in each monkey as a function of increasing cocaine dose.

Responding following the post-infusion pause began abruptly and was maintained throughout the remainder of the experimental session. Figure 2 presents the mean number of seconds and the mean number of responses needed to obtain successive blocks of 25 reinforcements once responding resumed following drug infusion. As depicted for the present DRL schedule in Figure 2, an overall time increase accompanied by an increase in responses reflect a shortening of inter-response times (IRTs), while a time increase and a constant or reduced number of responses indicate a lengthening of IRTs.

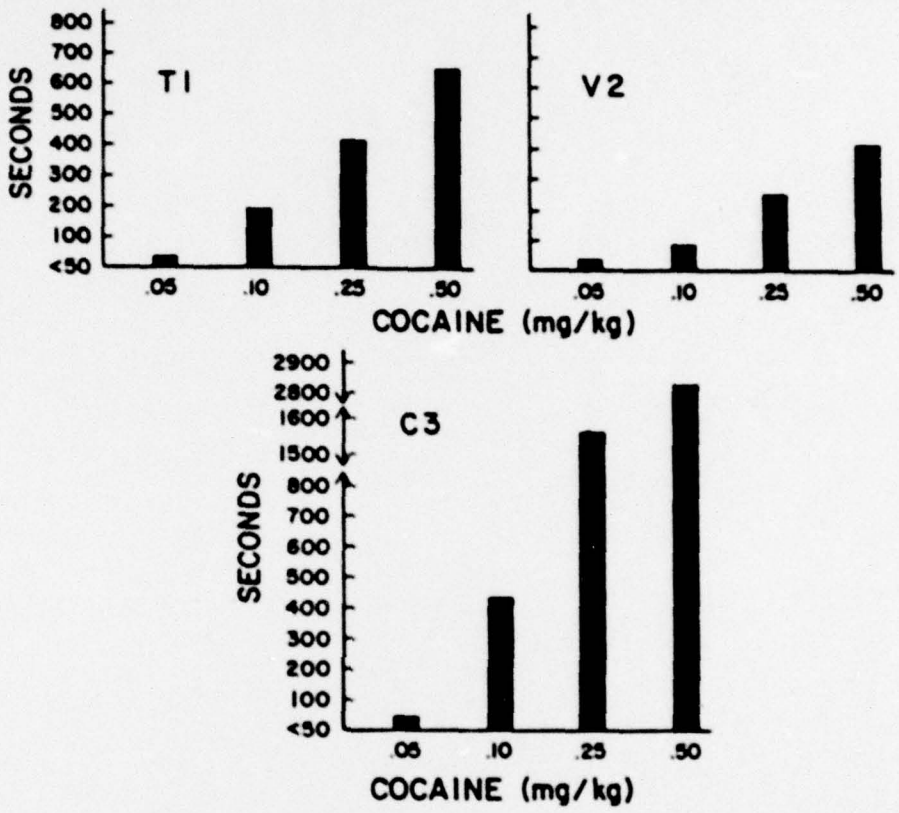

Fig. 1. Duration of post-infusion pause for individual monkeys as a function of cocaine dose. Post-infusion pauses of less than 50 sec were within the nondrug control range.

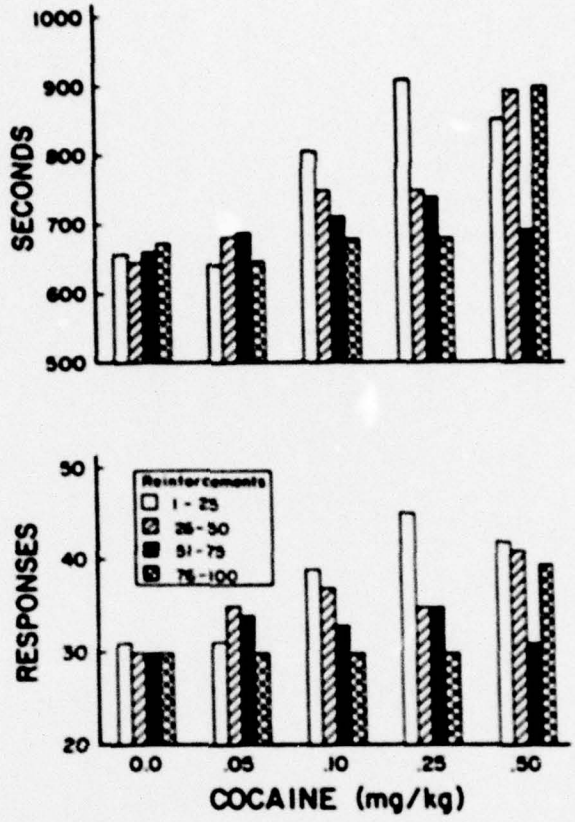

Fig. 2. Mean time and mean number of responses required by the three monkeys to obtain successive blocks of 25 reinforcements following infusions of different doses of cocaine. The mean times for reinforcements 1-25 were corrected for cocaine-induced post-infusion pauses.

For example, when animals were infused with cocaine at a dose of 0.05 mg/kg neither the amount of time nor the number of responses required to obtain the first block of 25 reinforcements differed from baseline. However, there was an increase in both time and number of response for the second and third block of 25 reinforcements. For the fourth block of 25 reinforcements both time and response number again reflected baseline conditions. Thus, at 0.05 mg/kg a cocaine-induced behavioral disruption, in the form of shortened IRTs, began to occur mid-way through the session and dissipated prior to the end of the session.

At doses of 0.10 and 0.25 mg/kg, a drug-induced decrease in IRTs occurred across the first three blocks of 25 reinforcements. The magnitude of this effect gradually lessened up to the final block of reinforcements where behavior returned to baseline conditions. Finally, when cocaine was infused at the highest dose of 0.50 mg/kg there was a shortening of IRTs throughout the session. However, as can be seen in Figure 2, the behavioral disruption at this high dose did not proceed in an orderly manner. Visual inspection of cumulative response records obtained at the 0.50 mg/kg dose revealed bursts of responding mixed with sporadic pauses of varied duration which began to occur during the second block of 25 reinforcements.

DISCUSSION

The data obtained in the present experiment reveal a bi-component, dose-dependent effect of cocaine on food maintained operant behavior. Immediately following cocaine infusion there was a dose-related complete cessation of responding which began and terminated abruptly. Once resumed, responding continued throughout the session but evidenced a dose-related behavioral disruption in the form of shortened IRTs.

The rather dramatic pause in ongoing behavior following cocaine infusion appears to be a unique general characteristic of cocaine-behavior interactions. Nearly all published research on the self-administration of cocaine has found that dose-related periods of non-responding follow drug infusion[1,6]. Additionally, several researchers have reported that the infusion of cocaine produces a dose-related pause in the performance of a food or water reinforced operant response[5,6,7].

The manner in which drugs and behavior interact is typically influenced by the nature of the experimental situation and, to a large extent, by the schedule of reinforcement. However, the cocaine-induced post-infusion pause appears to be little influenced by variables other than drug dose and is not a reliably observed characteristic of other CNS stimulant drugs.

On the other hand, the cocaine-induced shortening of IRTs obtained in this experiment is in complete accord with the effects of other stimulant drugs on DRL behavior[8,9].

To date, the majority of published research dealing with cocaine and behavior has used a drug self-administration procedure. Under this procedure opiates, barbiturates and stimulants are easily distinguished by: the manner in which organisms acquire the responses terminating in drug reinforcement, the patterning of drug administration, and the behavior exhibited when the drug is withheld. Cocaine self-administration closely resembles the self-administration of other CNS stimulants. However, cocaine differs from other CNS stimulants with respect to the biochemical mechanisms which produce its behavioral effects[10]. The post-infusion pause data obtained in this experiment suggest that there may also be some qualitative differences between cocaine-behavior interactions and those drug-behavior interactions found with other CNS stimulants.

One possible explanation for the obtained results would be in terms of cocaine's effects on the CNS. Cocaine stimulates the CNS from above, downward. Following cortical stimulation, an increase in cocaine dose results in stimulation of lower motor centers. Indeed, higher centers can be in a stage of post-stimulation depression while lower centers are in a

stage of excitation[11]. The sequential nature of CNS stimulation by cocaine may be taken as analogous to the sequential behavioral effects found in this study. Such an analogy would imply that the post-infusion pause reflects initial cortical stimulation and the subsequent effects on behavior reflect increased involvement of stimulated lower centers.

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